POINTS TO CONSIDER

Protocol: Use of double marking with retroviral vectors to determine rate of reconstitution of untreated and cytokine expanded CD34+ selected marrow cells in patients undergoing autologous bone marrow transplantation

SCIENTIFIC ABSTRACT

Autologous BMT in is frequently used as consolidation or salvage therapy in pediatric malignancy to allow administration of intensive chemotherapy where hemopoietic suppression would otherwise be dose limiting. This increased dose of chemotherapy and radiation therapy may allow a higher proportion of patients to be cured than would be possible with conventional therapy. One of the major causes of morbidity after autograft is the risk of infection and bleeding during the period of pancytopenia which follows the administration of ablative chemotherapy. One way of improving autologous stem cell rescue is therefore to shorten the period of aplasia which follows the procedure and thereby reduce the morbidity and mortality. A second improvement would be to harvest as few stem cells as possible. One way to achieve both these aims is by expanding committed and uncommitted progenitor cells ex vivo.

We and other investigators have evaluated the ability of growth factors to expand CD34 enriched marrow cells ex-vivo and noted little expansion of the most primitive cell populations (appendix A). While growth factor treated marrow may therefore produce earlier engraftment, its capacity to produce long term reconstitution remains unknown. There is a concern that the use of mo extensive growth factor combinations, whose activities reached further back in hemopoiesi.., would differentiate rather than expand or maintain true stem cells. If so, such marrow would produce earlier reconstitution but at the expense of being unable to contribute to long term engraftment

The ideal of ex vivo expansion is to increase both committed and non-committed progenitor cells thereby accelerating initial engraftment and ensuring sustained reconstitution. An acceptable alternative is simply to expand committed progenitor cells to reduce the period of post transplant aplasia provided sufficient pluripotent stem cells were retained in an undifferentiated state to permit long term recovery. Gene marking of marrow ex vivo allows determination of whether adequate numbers of stem cells remain in vivo. In this study we plan to use genetic marking of marrow ex vivo with two distinct vectors to compare the subsequent in vivo reconstitution of two aliquots of CD34 selected marrow - one treated and one unmanipulated. This protocol will therefore answer questions about the feasibility of accelerating hemopoietic reconstitution and the impact of such action on uncommitted progenitor cells. It will be a generic processing and transduction protocol for patients receiving autologous BMT for pediatric malignancy.